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Primer on Psoriatic Arthritis

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Introduction

Psoriatic Arthritis (PsA) is a complex inflammatory disease with heterogenous clinical features which complicates skin/nail psoriasis (Pso) in up to 30% of cases. There are no diagnostic criteria or tests. Diagnosis is most commonly made by identifying inflammatory musculoskeletal (MSK) inflammation of the joints, entheses or the spine in the presence of skin and/or nail Pso and in the usual absence of rheumatoid factor (RF) and anti-Cyclic Citrullinated Peptide (aCCP). The main clinical, laboratory and radiographic features which distinguish PsA from other forms of arthritis are shown in **Table 1**.

As depicted in **Figure 1** the evolution from psoriasis to the point at which the patient meets the ClASsification criteria for Psoriatic ARthritis (CASPAR) classification criteria (described in classification section below) for PsA may occur in stages. PsA complicates Pso in up to 30% attending dermatology clinics. The link between skin and MSK inflammation is certainly established but the mechanism is unclear. Many PsA patients with active disease may have very little Pso and the same may be said in reverse relating to severe Pso. One hypothesis is that this heterogeneity may be explained by differences in genotype, especially in the HLA region (referred to in section on Mechanisms/Pathophysiology below).

In recent years, new targeted therapies for PsA have been approved with additional therapies in development. These developments have substantially improved both short-and long-term outcomes including a reduction in MSK and skin manifestations as well as radiographic damage. These new treatments are at least in part related to improved understanding of the genetic basis of PsA and the underlying molecular pathways which are activated and contribute to disease expression. For example genetic studies have confirmed the association of PsA with single nucleotide polymorphisms (SNPs) in the IL17/IL23 pathway[1,2] with added significance of these findings being supported by immunopathologic studies which demonstrate the predominance of IL17-expressing CD8+T-cells in PsA synovial fluid.[3] Treatments targeting IL17 and IL23 have proven particularly effective for skin Pso but are also effective and licensed for MSK manifestations. It is hoped that with efforts underway aimed at improving our understanding of the molecular basis for the heterogeneity of PsA, that a precision medicine approach to treating PsA may not be too far away.

Epidemiology

While the prevalence of PsA among patients with Pso has been estimated as 23.8% in a recent meta-analysis when CASPAR (described in classification section below) is applied, the incidence of PsA among patients with Pso ranges from 0.27 to 2.7 per 100 person years, depending on the study and outcome definition.[4] PsA is relatively uncommon in the general population (0.10-0.25% of adults).[5] The prevalence of PsA is highest among patients within the age range of 30-60 and is overall equally common among men and women.[6] The majority of patients with PsA are white. It is unclear whether this is related to a specific genetic underpinning or perhaps in part related to the difficulty in identifying Pso among patients with darker skin colours.[7] Of interest, the reported

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prevalence of PsA is lower in Asia than in Europe and North America, potentially suggesting differences by race and/or ethnic group or by environment.[5]

The prevalence and phenotype of PsA is quite different among children, in part related to differences in classification criteria. Within the International League of Associations for Rheumatology (ILAR), classification criteria for PsA and enthesitis-related arthritis are analogous to the CASPAR and ASAS criteria used in adults but they are quite different in that a variety of exclusion criteria move patients to other categories depending on certain factors.[8,9] For example, a patient with HLA-B27, a first degree relative with HLA-B27-associated disease, a positive rheumatoid factor, or a systemic presentation of JIA would be excluded from having a diagnosis of PsA[9] (**Table 2).** The ILAR criteria are the most commonly used criteria, however, an alternative juvenile PsA, the Vancouver Criteria, were developed in 1989 though are rarely used today. [10,11] Additionally, limitations with the ILAR criteria include that: (1) patients are required to have a diagnosis of psoriasis to be classified as juvenile PsA. This is not withstanding the fact that approximately half of patients with juvenile PsA develop their arthritis first and later develop psoriasis, further complicating classification criteria development in children;[12] and (2) the criteria refer to boys/men when we know that PsA affects both sexes in equal proportion. Treatment for JIA may differ from treatment of adult PsA. Methotrexate remains the first line therapy as of 2019, although a 2021 update of the ACR JIA treatment guidelines are in progress.[13] Many therapies used to treat adult disease have not yet been approved for use in children.

A number of potential risk factors for the development of PsA have been identified among patients Defining PsA in a population is challenging and one of the potential reasons that prevalence estimates vary by study. CASPAR criteria are ideal for studies in which patients are being examined.[16] However, studying small samples (i.e., a dermatology clinic) can be associated with selection bias, leading to biased prevalence estimates. On the other hand, studying large, population-based datasets are complicated by misclassification bias as they rely on codes for defining PsA (i.e., missing diagnoses that have not been recorded in the dataset and simultaneously misdiagnoses of PsA as having conditions unrelated to Pso such as osteoarthritis).[15,17,18] The truth may be somewhere in the middle. Thus, both study designs must be interpreted in light of these potential limitations although they are helpful in understanding not only prevalence and incidence but also outcomes and risk factors for PsA.

Comorbidities

PsA is associated with several chronic conditions that may impact both quality and quantity of life.[19] While most studies show that the overall mortality in PsA is not higher compared to the general population, mortality from CV comorbidities and psychiatric disease seem to be higher.[20] Obesity is particularly common in PsA, significantly more prevalent than in patients with psoriasis, rheumatoid arthritis or compared to those in the general population.[20] Obesity can significantly impact function, quality of life and response to therapy.[21] In addition, PsA is associated with a higher prevalence of cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes, and the combination of these, metabolic syndrome. It should come as no

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surprise then that PsA is also associated with an increased incidence of cardiovascular events such as myocardial infarction, even after adjusting for traditional risk factors.[22] Similarly, patients with PsA are at significantly increased risk for diabetes and fatty liver disease.[23,24] These cardiometabolic conditions may also be associated with increased disease activity.[20] Beyond cardiometabolic disease, depression and anxiety are common in PsA, affecting 10-30% each, [25] and fibromyalgia/central sensitization is also common, affecting nearly 30% as well.[26,27] Depression, anxiety and fibromyalgia have a substantial impact on treatment outcomes and should be identified and managed so as to improve outcomes.[28,29]

PsA is also associated with extra-articular manifestations including uveitis and inflammatory bowel disease (i.e., Crohn's disease and ulcerative colitis).[30] In a recent meta-analysis, the prevalence of uveitis and IBD were each approximately 3%.[31] These conditions can have a significant impact on treatment selection as not all therapies for PsA cover these manifestations (see treatment section below).

Mechanisms/Pathophysiology

PsA is a complex genetic disease

There is a strong genetic contribution to both Pso and PsA. While epidemiologic evidence suggests that the recurrence rate of PsA among first degree relatives of PsA probands (λs 30 to 48) is greater than the recurrence of psoriasis among first degree relatives of Pso probands (λs 4 to 10) [32], a more recent study, which interrogated SNPs from large-scale genotyping arrays, while confirming strong heritability, concluded that there is perhaps a stronger contribution coming from Pso. [33] The genetic associations in PsA are with both HLA- and non-HLA-region genes with the strongest association being within the HLA region. HLA-C*06:02 is found in ~60% of those with Pso but the frequency is significantly lower at 28% in those with PsA [34] This same study reported that 18% of PsA cases were HLA- B*27 positive, with the frequency of B*27 in PsC (Pso patients where PsA has been excluded) no different from the normal controls. HLA- B*08 was the major allele at 37% in PsA but interestingly, its frequency was significantly reduced in PsC to 15%. When HLA alleles and amino acid sequences were compared between PsA and PsC directly , the most significant association was found at HLA-B amino acid position 45. Of the amino acid residues at this position, glutamine (HLA-B Glu45) most significantly increased risk for PsA compared to PsC. Although, among the HLA alleles, HLA-B*27 had the lowest p value, the association was much less significant than the association with HLA-B Glu45. It is interesting that HLA-B alleles previously associated with PsA including HLA-B*27, -B*38, -B*39 have Glu at position 45.[35] Another study that also controlled for age of psoriasis onset, showed that HLA-C*06:02 is not associated with PsA and that amino acid position 97 (asparagine or serine) of HLA-B differentiates PsA from PsC. Of note, HLA-B*27 has asparagine at position 97, and HLA-B*07 and HLA-B*08, serine.[36]

HLA-class 1 molecules play a critical role in our immune responses, particularly to viruses, by presenting viral peptides to CD8+T cells. There is accumulating evidence for a role of CD8+T

cells in PsA pathogenesis [37] with clonally expanded populations found in synovial fluid and tissue. The amino acid residues associated with PsA are in the antigen binding grove of the HLA-B molecule. The peptides driving clonal expansions of CD8+T cells in PsA have not been identified but given the structural similarity of the binding (B) pockets of each of the HLA-B molecules associated with PsA producing a negative charge, it is highly likely that the peptide sitting in the B pocket has positively charged amino acids at position 45.[38] It has further been suggested that the heterogenous nature of this T cell response determines the molecular pathways which are activated and which ultimately result in characteristic diverse clinical disease expression and perhaps treatment responses. In support of this concept, studies have shown associations of HLA genotypes not just with susceptibility to disease but also with certain disease features such as the interval between the onset of Pso and PsA (HLA-B*27 being associated with a short interval between skin and musculoskeletal disease and HLA-C*06 with a longer interval), dactylitis (B*27:05:02-C*01:02:01, B*08:01:01-C*07:01:01 haplotypes), enthesitis (B*27:05:02-C*01:02:01 haplotype) and sacroiliitis (symmetric- B*27:05:02-C*01:02:01 and B*27:05:02-C*02:02:02 haplotypes; asymmetric (B*08:01:01-C*07:01:01 haplotype). [39]

Genetic and genomic risk factors- genes proteins and pathways

While the strongest genetic associations with PsA are with genes within the HLA region, non-HLA gene associations are also well described. Many of these genetic risk loci reported as associated with PsA susceptibility are shared with psoriasis such as *IL12B* and *TRAF3IP2*, involved in IL17 signalling [40], perhaps reflecting shared molecular pathways mediated by the presence of cutaneous psoriasis in both phenotypes. It is also possible that the number of shared susceptibility alleles relates to inadequate exclusion of MSK inflammation in patients designated as PsC. A number of PsA-specific loci have however been identified thus beginning to explain the additional MSK burden. These loci include the presence of glutamic acid at the amino acid position 45 in HLA-B, a risk locus at chromosome 5q3, distinct PsA variants at the *IL23R* locus, *PTPN22* which is a potent inhibitor of T cell activation and *RUNX3* which is involved in CD8+ T lymphocyte differentiation and is therefore, a good candidate for involvement in PsA.[41] It is noteworthy that all of these PsA-specific loci involve genes which are involved in immune activation emphasising the importance of immune dysfunction PsA pathogenesis.

The exact mechanism which results in over-expression of pro-inflammatory mediators, including cytokines, is poorly understood. We do know however that active PsA is associated with production of a cascade of cytokines including TNFα, IL17 and IL23.[42] The importance of these cytokines in disease expression is supported by the significant efficacy of inhibitors of these cytokines on clinical disease expression. As not all patients respond to cytokine inhibition and as some disease features, such as Pso, respond better to strategies targeting cytokines of the IL17 or IL23 pathway, it has been suggested that improved understanding of the molecular pathways associated with specific disease features may help to better guide treatment choices. [37]

Environmental factors

A number of environmental factors are thought to be associated with the development of PsA. These include musculoskeletal injury, obesity and infection; evidence for association with stress or anxiety, alcohol consumption or with smoking is controversial. For years, support for a role of musculoskeletal injury was poor with case reports or series providing anecdotal evidence only. A recent matched cohort study using data from The Health Improvement Network showed that patients with Pso exposed to trauma, especially bone and joint trauma, had an increased risk of PsA compared with controls.[43] Association with trauma is not confined to major trauma consistent with the hypothesis that microtrauma at entheseal sites may be a critical disease initiating factor.[44] It is possible that this may explain the association of PsA with increasing BMI [45] with higher mechanical load at entheseal sites being a consequence of high BMI. It is also possible that the effects of excess adipose tissue, which includes abundant pro-inflammatory mediators, may spill over to other tissue sites.

A role for infection in triggering PsA has been suggested in particular with the well-known association between streptococcal infection and guttate Pso. Both Pso and PsA also occur more commonly and severely in the presence of HIV disease which targets CD4+ and not CD8+T cells. There have been some studies too which have examined changes in microbiome and onset of PsA [46] which to date have been inconclusive. This is clearly an area for further research focus as microbial-driven populations of IL17-producing innate immune cells have been identified in other tissues [47] and a recent study very nicely demonstrated the considerable influence of the gut microbiota—together and over time—on systemic immune cell dynamics.[48]

PsA pathogenetic mechanisms

Although the sequence of events leading to the onset and progression of human PsA has not yet been delineated, it is proposed that the arthritis is triggered by a complex interplay between a subject's genetic predisposition and environmental influences described above that trigger an immune response leading to entry and proliferation of immune cells at articular, peri-articular, and extra-articular sites. Given the strong association with HLA class I alleles and Th17 immune response, a model for pathogenesis of PsA was recently proposed whereby primed antigen-presenting cells at sites such as the skin or enthesis engage with innate lymphoid cells and naive T cells, leading to local clonal expansion of type 1 cells (T helper 1 (TH1) and type 1 CD8+ (Tc1) cells) and type 17 cells (TH17 and type 17 CD8+ (Tc17) cells).[49] The interplay between the effector T cell subsets, stromal cells, and the cytokine milieu at the local sites determines disease features including enthesitis, synovitis, bone and cartilage loss as well as new bone formation in the axial and peripheral musculoskeletal (MSK) system.[49]

The strong relationship between skin and MSK inflammation begets the question whether the relationship between inflammation at the two sites is successive (changes in the skin triggering MSK inflammation) or synchronous (a common trigger leading to skin and MSK inflammation). In 70% of patients with PsA, skin inflammation predates MSK inflammation by many years. This latency if associated with certain HLA alleles- HLA C*0602 is associated with a long duration between skin and MSK inflammation.[50] Thus, mediators originating in the inflamed skin could trigger MSK inflammation. This theory is supported by a recent study that demonstrated increased

circulatory skin derived tissue resident memory CCR10+ CD8+ T cells in the peripheral circulation of PsA patients compared to patients with PsC.[51] However, these cells were not enriched in the synovial fluid.[51] Another study has demonstrated a high proportion of synovial Tc17 cells expressing markers typically associated with homing to the skin or gut.[52] Injury to sites of biomechanical stress may be the underlying mechanism driving synchronous skin and MSK inflammation. It has been demonstrated that in 30% of patients, joint disease occurs simultaneously or prior to onset of skin disease.[42] HLA- B*27 is associated with such short skin-joint disease latency.[34,39] Microtrauma at sites of significant biomechanical stress leading to enthesitis may underlie this form of PsA with skin disease limited to sites of microtrauma such as behind the elbows and knees and joint disease triggered at the enthesis. In fact, it is believed that 'enthesitis' may be the mechanism underlying the diverse MSK manifestations of PsA/SpA including eye and gut inflammation. The association between HLA-B*27 and more severe sonographic enthesitis in PsA supports this hypothesis.[53]

Clonal expansion of T cells in the psoriatic joint is well described.[54,55] A recent study demonstrated a 3-fold expansion of memory CD8 T cells in the joints of PsA patients compared to peripheral blood, as well as pronounced CD8 T cell clonal expansion.[56] These cells express cycling, activation, tissue-homing and tissue residency markers, including the skin/gut-homing marker ITGA1 (CD49a) and granulysin. The chemokine receptor CXCR3 is upregulated in the expanded synovial CD8 T cells, and its two receptors CXCL9 and CXCL10, are elevated in PsA synovial fluid.[56] Elevated CXCL10 is known to predict future development of PsA in patients with PsC.[57] To summarize, inflammation in the MSK structures in patients with Pso is most likely triggered in genetically susceptible hosts by environmental factors such as trauma, infections or even changes in the microbiome that then leads to expansion of immune cells of both the innate and adaptive systems. The mediators for MSK inflammation may be skin derived or there may be a common trigger causing skin and joint disease. These events may lead to expansion of CD8 T cells well as other effector cells of the innate and adaptive systems. The local tissue milieu likely drives the specific disease manifestations synovitis, bone and cartilage loss as well as new bone formation. These concepts are illustrated in Figure 2.
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Diagnosis, Screening and Prevention.

The first step in caring for patients with PsA is to make an accurate and timely diagnosis allowing future therapy. The process of diagnosing PsA brings multiple pieces of evidence together to assign a particular disease label. Typically, these may include patient history, physical examination and results of laboratory and imaging results. Although the diagnostic process may end in a clinician making a binary decision (either the disease is present or not), this

is often associated with a level of probability of the diagnosis and other potential differential diagnoses.

The majority of patients manifest psoriasis before developing PsA, although this may not have been previously diagnosed. In patients with psoriasis, the key issue is to identify whether inflammatory MSK disease (arthritis, enthesitis or spondylitis) is present. The majority of patients with inflammatory arthritis and Pso are likely to have PsA.

Unfortunately, there is a well-recognised delay in diagnosis typically seen in patients with PsA. Recent data from a United Kingdom (UK) national audit in 2015 estimated this to be a median of 29 weeks, and significantly longer than matched patients presenting with RA.[58] This delay has also been shown to have significant implications. A further UK study found that a delay in diagnosis of 12 months was associated with increased physical function impairment at 10 years follow up despite active treatment.[59] A subsequent study in Ireland showed that even a delay in diagnosis of 6 months was associated with a higher chance of peripheral erosive disease and poorer physical function.[60]

Clinical presentation

There is relatively little data concerning the signs and symptoms that aid diagnosis of PsA. In 2013, a nominal group exercise was performed with health care professionals interested in rheumatology, but also patient research partners to identify descriptive elements of inflammatory joint disease. Symptoms identified included early morning stiffness (EMS) >30 minutes, joint tenderness, pain aggravated by rest and relieved by exercise, symptoms improved by non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroid use, joint erythema or warmth and related fatigue. Possible clinical signs included joint swelling, limited motion and joint deformity.[61]

In terms of peripheral arthritis, presentation is similar to most forms of inflammatory arthritis although the pattern of joint involvement can vary with oligoarticular and polyarticular patterns described. DIP joint involvement is more common than in other forms of inflammatory arthritis. The clinical presentation of MSK inflammation can be helpful to differentiate between PsA and other forms of inflammatory arthritis (table 1). In addition to peripheral arthritis, patients often present with inflammation in other musculoskeletal tissues including at the insertion of a tendon into the bone (enthesitis), seen in up to 67% of presenting cases,[62–67] fusiform swelling of a digit with inflammation typically seen in multiple tissues (dactylitis), seen in 12-39% of cases [62–68] and axial involvement within the axial spondyloarthritis (AxSpA) phenotype seen in 5-28% of cases at diagnosis, but potentially up to 70% in late stage disease.[62–67] Although the vast majority of patients presenting with PsA have peripheral MSK involvement, a few cohorts have reported a prevalence of axial disease in isolation with psoriasis at 7-17%.[66,69]

Investigations

Part of the reason accounting for this diagnostic delay compared to RA may be related to a lack of specific investigations to confirm the diagnosis (table 1). Primary care physicians typically use inflammatory markers like C reactive protein (CRP) and specific antibodies like rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPA) to screen patients with possible inflammatory arthritis. PsA is usually seronegative, although a positive RF or ACPA does not exclude the

condition. At presentation, 33-89% are identified as having a raised CRP [62,64,69,70]; thus, a significant proportion of patients do not have raised blood markers despite active disease.

Although typical imaging features in PsA have been identified, and are included in the classification criteria, these are more prevalent with increasing disease duration. In early disease, radiographs are often normal as bony damage has not occurred, so often do not assist in diagnosis. A study in 2003 of peripheral arthritis identified that 27% of patients had erosions at presentation, and 10 years later in the Tight Control of PsA (TICOPA) study, results were similar.[71] However, in both studies, the amount of erosive disease seen is relatively small and affecting only a few joints in most of the patients imaged.

Given the potential for axial involvement, imaging of the spine and sacroiliac joint can also show abnormalities in PsA. Again this is more prevalent with increasing disease duration with limited value in early diagnosis.[72,73] Sacroiliac joint involvement in PsA appears similar to that seen in AS although asymmetrical sacroiliac involvement is more common.[74,75]

Classification

Related but independent from diagnosis, is the issue of classification. Classification is the method of defining a disease for research. This allows standardisation across the field, rather than taking into account multiple different inputs which may feed into diagnosis. In classification, it is specificity that is key to ensure homogeneity in clinical studies even though sensitivity may suffer in this situation.

The first classification criteria developed for PsA were the Moll & Wright criteria, which were developed based on clinical observation. They have been the key criteria used until around 2006 and are simple stating that PsA is an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis) in the presence of psoriasis and with the (usual) absence of serological tests for rheumatoid factor (RF).[76] However they focused on peripheral arthritis rather than other aspects of the musculoskeletal disease such as enthesitis and required a negative rheumatoid factor test which was an issue for a minority of patients.[77]

Over the decades, there have been a number of other classification criteria developed but until the advent of the CASPAR criteria, none of these were utilised widely in clinical research.

In 2000, a large international consortium of rheumatologists came together to develop new robust and data-driven classification criteria which were finally published in 2006. The CASPAR criteria bring together a wider range of items for inclusion, overlapping with the Moll & Wright criteria but also allowing classification of people without Pso (approximately 10%) or with a positive RF (approximately 15%) provided they have other key features of the disease.[16] In the development cohort, these had high sensitivity and specificity,[16] and this has been confirmed in numerous independent studies subsequently.[78–80]

In early disease, the classification may not be quite as straightforward but still specificity has been confirmed as typically over 95%. The issue in early inflammatory arthritis is that there seems to be lower sensitivity as some typical features may not yet be present.[65,81] In particular, typical new bone formation is not common at presentation therefore limiting the ability to identify the disease.

Another issue raised with the CASPAR criteria is the heavy weighting given to current Pso. Whilst the majority of patients do fulfil this criteria, it does make the criteria much harder to fulfil if a patient's Pso has been treated and gone into remission. Potentially, a clear diagnosis of psoriatic skin or nail disease by a dermatologist could be given similar weighting as current active psoriasis. The next step proposed for the CASPAR criteria is most likely to involve clarification of the "stem" of the criteria which state that patients must have Inflammatory articular disease (joint, spine, or entheseal). From the rheumatology perspective, where we are trying to identify PsA amongst other patients with inflammatory arthritis, this is straightforward. However, for dermatologists and primary care physicians, the key issue is how to identify inflammatory articular disease in patients who have known psoriasis.

Prognosis

Predicting prognosis in PsA is also based on limited data with significant individual variation. Multiple studies have shown that the evolution of PsA can vary over time with different joint and extra-articular involvement. The pattern of peripheral joint disease does seem to change over time, with oligoarthritis more common in early disease cohorts. In most cases, increased joint involvement is seen over time with increasing disease duration with a high proportion of mono or oligoarthritis progressing to polyarthritis.[82,83] Involvement of other domains can also change over time, in particular axial involvement is increasingly common with increasing disease duration.[84,85] However axial spondyloarthritis, and specifically axial PsA can be difficult to identify and clear evidence of axial involvement with radiographic change and restriction of mobility is likely to take many years to develop.

A number of treatment recommendations have noted potential poor prognostic markers based on the literature to aid treatment decisions. In terms of peripheral arthritis, in particular, these relate the number of joints involved (polyarthritis or ≥5 joints), presence of dactylitis, high inflammatory markers (CRP) or baseline erosive disease.[86,87] However, there is insufficient evidence around these risk factors and it is not easy to predict prognosis for individual patients. Many of these studies have focused solely on radiographic damage as the poor outcome of interest which also affects the predictors of prognosis. Overall, while oligoarthritis is less likely to cause radiographic damage within the hands or feet, it may have a significant impact on quality of life and functional ability.[88]

Screening

Unfortunately, there is often a significant delay in the diagnosis of PsA even though the majority of patients have a preceding condition in the form of skin Pso. Up to 30% of patients with Pso may go on to develop PsA. Although predicting this accurately at the individual level is not currently possible, studies have identified key predictors of PsA development including severity and site of psoriasis (nails, scalp), obesity, smoking and trauma.[15] Delay in diagnosis may be a particular issue in patients presenting with limited disease (e.g. oligoarthritis) or involvement in other domains e.g. axial disease or enthesitis.

Given awareness of the delay in diagnosis and the associated consequences, there has been a push to support early diagnosis with education and interventions focusing on primary care physicians, dermatologists and patients. In particular, studies have attempted to address this using screening questionnaires to identify potential PsA patients usually amongst a Pso population. There are a number of screening questionnaires developed but their sensitivity and specificity can be problematic.[89,90] Comparative studies, for example the CONTEST study, have shown similar levels of sensitivity (74.5-76.6%) and specificity (29.7-38.5%) across different questionnaires,[89] and the CONTEST questionnaire, developed from a combination of the best performing questions within each questionnaire did not outperform the PEST questionnaire in a subsequent study.[91] Most studies show higher sensitivity and lower specificity as joint symptoms related to other diagnoses are common. Studies have also shown that it seems harder to identify patients with pure axial disease. Whilst screening tools are not perfect, some studies have found a reasonable benefit to using them and the PEST questionnaire, which is the shortest questionnaire available, is recommended annually for Pso patients in the UK.[92] They also indirectly provide education to patients with Pso who are then aware of the potential for development of a related arthritis.

Potential to prevent the evolution to psoriatic arthritis

In addition to supporting earlier diagnosis of PsA, recent research has also focused on the concept of a spectrum from psoriasis to PsA (Figure 1). This raises the potential of identifying disease or the high likelihood of disease before it clinically manifests. In collaboration between dermatology and rheumatology, studies monitoring patients with only psoriasis, aiming to predict development of PsA are underway. To date, these studies have predominantly confirmed known predictors of PsA development [93] but in larger populations, they might be used to develop predictive models that could be applied to individuals. This would allow in depth study of the pathogenesis of disease in a high-risk population and may elucidate the triggers involved in this continuum. Potentially, as in RA, interventional studies trying to prevent the development of disease could be established in high risk populations. Studies such as these will require collaborative efforts so as to recruit suitably sized populations and should include patient representation to ensure that individual patients are educated about their potential risk and what this may mean for them in the future.

Therapy of Psoriatic Arthritis

Introduction.

Prior to the year 2000, the pharmacologic treatment options for PsA were essentially limited to non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids methotrexate, sulfasalazine and cyclosporine. There had been few randomized therapeutic trials specifically in PsA. Despite known clinical differences between the conditions, there was a general assumption that the evidence from rheumatoid arthritis (RA) clinical trials could be extrapolated to PsA. Since the year 2000, the field of PsA therapeutics has been revolutionized due to several developments. These include 1) Numerous immunologically targeted biologic disease modifying drugs (bDMARDs)

and targeted synthetic drugs (tsDMARDs) have been developed for the treatment of systemic inflammatory autoimmune diseases, usually initially in RA. Testing of these therapies in other conditions, including psoriasis, PsA and axial spondyloarthritis (axSpA) also demonstrated significant efficacy. 2) Research on the immunopathogenesis of PsA has helped reinforce the rationale for effectiveness of targeted immunotherapies, and also suggested new treatments. 3) Research on the clinical aspects of PsA has led to increased appreciation of the complex and heterogeneous nature of the disease, with potential involvement in individual patients in peripheral arthritis, axial arthritis, enthesitis, dactylitis, spondylitis, skin and nail psoriasis, iritis and inflammatory bowel disease. These domains need to be assessed individually in order to assure that all are being treated adequately. 4) Development of reliable and validated outcome measures to assess PsA clinical domains has helped optimize assessment in clinical trials through the last two decades.[94] (Domains that are assessed and commonly used measures are noted in **Table 3**.)[95–97] 5) Advances in imaging, including ultrasound and MRI, have allowed more precise visualization of tissue inflammation and joint damage. 6) In addition to standard randomized controlled trials, strategy trials such as treatment to target of remission and head-to-head (H2H) comparative trials are increasingly being performed. The following is a focused summary of PsA pharmacologic treatment organized by specific classes of drugs, followed by a summary of treatment recommendations and treatment strategies. Review of non-pharmacologic therapies, including physical and occupational therapy, psychotherapy, and dietary approaches including weight reduction is beyond the scope of this manuscript. These treatments should be pursued in parallel with pharmacologic treatment.

Adjunctive Treatments: NSAIDs and glucocorticoids

NSAIDs.

NSAIDs are frequently used for symptomatic improvement of pain associated with arthritis and periarticular manifestations of PsA. Interestingly, and in distinction to the case with RA, there is very little evidence addressing NSAID efficacy specifically in PsA. In one 12 week randomized controlled trial (RCT) of celecoxib 200 or 400 mg statistical superiority over placebo was not demonstrated.[98] Nevertheless, many years of clinical experience suggests that they can be a useful adjunct for various domains of PsA, including peripheral arthritis, axial arthritis, enthesitis, and dactylitis. Indeed, in axial disease, the lack of efficacy of conventional synthetic DMARDs (csDMARDs) leaves NSAIDs as the mainstay of therapy. Before biologic agents, NSAIDs were commonly included as concomitant therapies in trials of DMARDs in PsA.

Glucocorticoids.

Glucocorticoids.
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Glucocorticoids.

Whereas topical steroid medications are commonly used to treat psoriasis and intra-articular steroids used to treat flares in one or a few joints, systemic steroids are not as commonly used in

PsA as in RA. In PsA, there is a need for caution when considering steroids for local tendon/entheseal injection, as efficacy over the longer term is questionable and tendon rupture has been reported. Part of the concern for steroid use in PsA comes from is the anecdotal experience wherein skin psoriasis can flare dramatically upon abrupt discontinuation of steroids, usually at very high doses.

Conventional Synthetic DMARDs (csDMARDs) (refer to Table 4[99])

Methotrexate. Although methotrexate (MTX) has been one of the most widely used medications for PsA in the last four decades, there have been very few studies of MTX in PsA.[100,101] Assessment of these few studies raised the suggestion that doses of MTX of 15 mg/week or higher may be more effective in PsA. In the Methotrexate in Psoriatic Arthritis (MIPA) trial published in 2012, no differentiation from placebo in the primary endpoint was observed.[102] However, design issues including the dose of MTX used impacted assessment of the data from that study, and MTX was effective in subset analysis of PsA patients who were more 'RA like' (i.e. polyarticular disease, with elevated acute phase reactants). In the Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) trial, MTX appeared to perform well, achieving levels of articular, enthesial and skin responses, numerically close to those achieved with TNF inhibition; of note, there was no placebo comparator.[103] Based on evidence from the SEAM study, as well as experience from global clinical practice, MTX remains an important therapy, especially in parts of the world with more limited health care resources. An additional benefit from MTX is that when used with certain biologic therapies, it can reduce immunogenicity. MTX can be associated with tolerability issues (e.g. nausea, diarrhoea, fatigue) and laboratory monitoring for safety issues (liver, hematologic) is necessary

Sulfasalazine. Sulfasalazine is an older oral medication that has shown to have modest efficacy in arthritis but no significant benefit for psoriasis was demonstrated in an RCT.[104] Gastrointestinal tolerability issues as well as allergic reactions may limit its utility, and laboratory monitoring (e.g. hematologic, liver) is standard.

Leflunomide. Leflunomide is an oral pyrimidine antagonist that has shown efficacy in arthritis endpoints in a single placebo-controlled study involving 190 PsA patients.[105] Less robust results were demonstrated in other domains of PsA, especially skin. Lab monitoring for liver function tests and blood counts is required.

Cyclosporine. Cyclosporine is a calcineurin inhibitor that has had greater use for skin psoriasis than in PsA, but can be effective for articular manifestations. Laboratory monitoring for renal toxicity is needed, and hypertension can limit its use in some patients.[106]

Biologic DMARDs

Tumour necrosis factor (TNF) inhibitors. TNF is a pro-inflammatory cytokine with myriad impacts on various aspects of the inflammatory and immune responses. TNF inhibitors (TNFi) represented a landmark breakthrough in the therapy of PsA. Following success observed in RA, the first evidence for this in PsA came from a trial demonstrating the effectiveness of etanercept in both articular and psoriasis domains.[107] Soon after, infliximab therapy was shown to improve articular and psoriasis domains, as well as physical function dactylitis and enthesitis; in addition,

treatment was shown to slow the progression of radiographic damage to peripheral joints in PsA.[108] Subsequently studied TNFi, including adalimumab, golimumab and certolizumab also showed efficacy across all PsA domains. All TNFi have also demonstrated benefit in ankylosing spondylitis, used as surrogate evidence for efficacy in the axial component of PsA. With the introduction of biosimilar versions of several TNFi in many countries around the world, the acquisition costs have decreased, an important consideration that impacts the utilization of biologic agents. Significant albeit infrequent serious side effects with TNFi include the risk of infection, including opportunistic infection (particularly tuberculosis) and autoimmune reactions.

IL-12/23 inhibition. Ustekinumab is a human IgG1 monoclonal antibody which binds to the common p40 subunit of IL-12 and IL-23, the former involved in differentiation and activation of Th1 cells and the latter in differentiation and activation of Th17 cells. By downregulating these pathways, a decrease of several key cytokines in the pathogenesis of psoriasis and PsA, including IL-23, IL-17, and TNF, may be seen. Its efficacy in PsA was confirmed in two phase 3 trials, across domains.[109,110] Of note, in dermatology, ustekinumab was the first biologic agent showing efficacy for skin psoriasis greater than that of TNFi. Ustekinumab failed to show benefit in ankylosing spondylitis,[111] although previously subjective axial symptoms did improve in a subset of PsA patients.[112] Whether axial arthritis in PsA differs from AS or the outcome measures used can detect improvement in extra-axial domains is a matter of discussion. The safety profile of ustekinumab is benign overall, with low rates of serious infection.

IL-17 inhibitors. IL-17 includes a family of related cytokines; IL-17 A and F appear to be the most involved in pathogenesis of inflammatory disease. IL-17 is produced by a wide variety of cells in the innate immune system such as natural killer (NK) cells, γδT cells, neutrophils, and mast cells which line barrier sites such as gut, skin and lung. Several, but not all of these cell types are activated by IL-23 produced by keratinocytes, macrophages and dendritic cells in response to microbial agents. IL-17 plays a role in preserving barrier function in the gut and integrity of the epithelium. Two IL-17A inhibitors are currently approved in PsA in many countries. Secukinumab is a human monoclonal IgG1 antibody that binds to IL-17A. All clinical domains of PsA demonstrated significant improvement, including particularly robust improvement in psoriasis and in axial disease in PsA .[113] Ixekizumab is an IgG4 humanized monoclonal antibody to IL-17A that has also shown efficacy in all clinical domains of PsA, similar to secukinumab. Both of these agents have conducted head-to-head trials against adalimumab, where skin psoriasis improved more with IL-17i and articular domains were comparable.[114,115] Brodalumab is a human antibody that binds to the IL-17 receptor, thus resulting in broad inhibition of the IL-17 family; it has been approved for psoriasis in many countries. PsA studies showed efficacy similar to the other IL-17 inhibitors.[116,117] Bimekizumab is a humanized IgG1 mAb that binds to IL-17A and IL-17F. It has shown efficacy in all clinical domains of PsA in a phase 2 study and is currently in phase 3 development.[118]

IL-23 inhibitors. The first IL-23i to be approved worldwide for PsA is guselkumab, a p19 IL-23 inhibitor that specifically targets IL-23 (distinct from ustekinumab which binds to the p40 unit and inhibits both IL-12 and IL-23). IL-23 is a key proinflammatory cytokine in psoriasis, and indeed,

its inhibition yields the most complete reduction of psoriasis manifestations compared to other biologics. Efficacy data for arthritis, enthesitis, and dactylitis domains of PsA is robust, similar to the data from RCTs of TNFi and IL-17i.[119,120] A sub-study of subjects with back pain and radiographic evidence of sacroiliitis demonstrated symptomatic improvement of spinal pain (BASDAI question 2).[121] This preliminary finding in patients with axial PsA will be further explored since studies of IL-23 inhibitors in ankylosing spondylitis failed to demonstrate separation from placebo, suggesting that this mechanism of action was not effective in axial inflammation.[122] Phase 2 studies of risankizumab[123] and tildrakizumab[124] demonstrated consistent with the phase 3 studies of guselkumab. There has been minimal signal for serious infection with IL-23i.

Costimulatory Blockade. Abatacept (CTLA4-Ig) is a recombinant human fusion protein which binds to CD80/86 on antigen presenting cells (APCs), preventing interaction with CD28 on T cells In a phase 3 trial in PsA. in which the majority of patients had failed TNF inhibition, modest benefit in arthritis and minimal benefit in psoriasis were noted.[125] Even though effect is modest, one advantage of the medication is its relatively benign safety profile.

Targeted Synthetic DMARDs

PDE4 inhibitor. The oral phosphodiesterase 4 (PDE4) inhibitor apremilast may downregulate a number of key pro-inflammatory cytokines involved in the pathogenesis of psoriasis and PsA, including TNF and IL-23. By inhibiting PDE4 apremilast was shown to have modest efficacy in treating psoriatic skin lesions, arthritis, and enthesitis/dactylitis.[126–128] It has a benign safety profile with no serious safety issues such as infection, and no need for laboratory monitoring

JAK inhibitors. The Janus kinase (JAK) – STAT kinase intracellular signalling system is critical for the induction of cellular activation by a number of cytokines involved in the pathogenesis of PsA, including IL-23, IL-6, and IL-15. There are 4 JAK molecules: JAK1, 2, 3 and TYK2. The first JAKi to be approved, tofacitinib, inhibits JAK3 and JAK1 more than JAK2.[129–131] Tofacitinib was effective in musculoskeletal domains and modestly beneficial for skin lesions. The safety profile was similar to that seen in treatment of RA, i.e. the risk of serious infection, the need for laboratory monitoring of liver function tests and blood counts, and rare side effect of lymphoma. Recent evidence suggests that thromboembolic events may occur when the medication is used in higher than recommended dose.[131] This may be a class effect. Other JAK inhibitors in development for PsA include the selective JAK1i, upadacitinib and filgotinib,[132,133] and the Tyk2i deucravacitinib.[134,135] Whether differential selectivity for JAK isoforms impacts efficacy across domains of PsA or toxicity remains to be seen.

Treatment Strategies

Treat-to-target. As in other fields of medicine, it has become commonplace to strive for a treatment target of remission, if possible, or low disease activity if not. Such a strategy yields optimal short and long term outcomes for the patient. Numerous "treat-to-target" (T2T) trials have been conducted in RA, utilizing quantifiable measures of disease activity, typically including numerically assessed physical examinations, such as joint counts, quantified patient self-assessment, and laboratory measures of disease activity, such as C-reactive protein. The TICOPA

Commented [AO1]: Place holder for phase III since that will likely be public by the time this is published?

Commented [PM2R1]: Phase 3 publications not out yet. Phase 2, including 1 year data, has been submitted for publication, thus the reference to the abstract

trial,[71] conducted in early PsA patients, compared patients evaluated monthly and requiring intensification of treatment if a goal of Minimal Disease Activity (MDA) activity was not met to patients seen every 3 months, without such a target of treatment. After 48 weeks, the patients in the T2T group demonstrated superior treatment results, thus supporting this goal of treatment in clinical practice. It is worth noting that many T2T studies are tautologic, insofar as the requirement to alter therapy to achieve a goal, results in greater achievement of the goal using similar metrics. Longer term outcomes, safety considerations, and pharmacoeconomic assessments should also be factors in therapeutic decision making.

Treatment Recommendations. Three international organizations have published and updated PsA treatment recommendations: the Group for Research in Psoriasis and Psoriatic Arthritis (GRAPPA), the European League Against Rheumatism (EULAR), and American College of Rheumatology/National Psoriasis Foundation (ACR-NPF). The GRAPPA recommendations[136] are developed by both rheumatologists and dermatologists as well as PsA patients and are organized across the domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis and nail psoriasis, as well as IBD and uveitis. The EULAR guidelines[137] yield overall similar recommendations as GRAPPA, but arranged in an algorithmic sequence from early and/or mild disease to more advanced disease wherein previous treatments have failed. The ACR-NPF guidelines[138] used a strict Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach. The guidelines chose one class/group of medicines ahead of another, allowing for variances depending on contextual factors, such as the presence of more severe skin disease. One key difference among the 3 guidelines is the recommendation to use TNFi prior to use of csDMARDs, based on both efficacy and safety data from clinical trials. In the absence of H2H trials available when these guidelines were developed, the majority of recommendations are considered "conditional", since the comparative evidence is indirect. It should be noted that there are also additional regional and societal guidelines, developed with less rigor, which present the clinician with a heterogeneous group of treatment guidelines to follow.

Conclusion. There are now numerous biopharmacologic therapeutic options for the management of PsA. Efficacy, with most of the options, has the potential to be significant in all clinical domains of the disease. However, in many patients, cross-domain efficacy can be variable, efficacy may not be achieved or soon lost and true remission is not frequent. Clinicians must assess each domain on a regular basis and aim to achieve remission or low disease activity across the different active domains, whilst being cognisant of potential adverse events. Greater understanding of the pathophysiology of the disease has allowed us to more precisely target the appropriate cellular and cytokine pathways of disease. Treatment effect with any single agent may wane, thus the need for multiple classes of medicine and choices of individual agents to switch to in order to sustain treatments targets remains necessary.

Quality of life

PsA has a significant negative impact on physical function and Quality of Life (QoL). The concept of QoL extends beyond the physical manifestations of disease to include emotional well-being,

self-esteem, participation in work and activities as well as non-health issues such as financial security, spiritual well-being, and environmental safety **(Figure 3).** PsA has a similar impact on QoL to that seen in RA despite generally being a less destructive arthropathy. The impact in PsA appears to be due to the accumulated burden of skin, joint, entheseal, axial disease, comorbidities and flare.[139,140] A consistent finding across qualitative studies has been the ranking of pain as the top priority for patients as an outcome for treatment but fatigue, physical function, ability to work and social participation all rank highly.[141,142] A recent observational study in early PsA and RA has shown that despite more severe disease at diagnosis near normalisation of health related QoL is seen in patients with RA after five years but not PsA, possibly due to delay in diagnosis.[143] Despite the presence of psoriasis as a visible risk factor for developing PsA in the majority of cases delay to diagnosis of PsA is longer than RA and is associated with worse clinical and functional outcome.[59,144]

Disease specific and generic assessment of QoL

The understanding of treatment outcomes important to patients has advanced considerably in recent years. It is clear that improving QoL is a high priority outcome from treatment to patients.[142] The assessment of QoL is recommended in all Randomised Controlled Trails (RCT) and observational studies of PsA.[145] Instruments for measuring QoL may be generic, applicable across diseases or the general population; or disease specific, attributing to the particular disease under consideration. Disease-specific QoL instruments cover concerns that are specific and relevant to the group of patients with the condition. Generic measures of QoL commonly used in PsA include the Medical Outcome Study Short Form 36 Item (SF36)[146] and the EuroQoL-5D[147]. The SF36 scores in eight subdomains and aggregates into two summary domains of physical and mental health and has data supporting its validity in PsA.[96] The EQ5D is available as an index (with country specific adjustments) or Visual Analogue Scale (VAS). Disease specific instruments include the Psoriatic Arthritis Quality of Life Index (PsAQoL)[148] and more recently the Psoriatic Arthritis Impact of Disease score (PSAID).[141] The PSAID has been provisionally recommended by Outcome Measures in Rheumatology (OMERACT) for RCT's and observational studies in PsA.[149] The PSAID can be used in the 9 or 12 item versions and captures information in 0-10 numeric rating scales of pain, fatigue, skin, work, function, discomfort, sleep, coping, anxiety, embarrassment, social participation and depression individually and in a summary score.

Impact of PsA on Personal and Professional life

With the development of improved patient reported measures of QoL such as the PSAID it has recently been possible to undertake large observational studies to quantify impact of disease on QoL. A global study of 1286 patients from eight countries identified high levels of residual disease impact despite being on treatment including; moderate/major impacts of PsA on physical activity (78%), ability to perform certain activities (76%), work productivity (62%), and career path (57%).[150] Skin/nail symptoms occurred in 80% of patients. Overall, 69% of patients reported that PsA had a moderate/major impact on emotional/mental wellbeing, 56% on romantic relationships/intimacy, and 44% on relationships with family and friends. Social impacts included emotional distress (58%), social shame or disapproval (32%), and ceased participation in social

activities (45%).[150] The relative impact of each domain of disease is uncertain. Evidence suggests that joints and pain are most strongly associated with reduced QoL in people living with PsA but that resolution of skin disease is required for optimal QoL. Pain from joint disease is often ranked as this highest priority to patients and was the highest ranked outcome in the PSAID development studies and a UK multicentre study.[141,142] However improving skin and joint disease symptoms are important to achieve optimal improvement in QoL.[151,152]

Financial burden on individual and society

Patients' experience of the disease vary considerably. One of the concerns of patients is the financial impact of the disease.[145,153] Even psoriasis alone has a significant impact on socioeconomic status.[154] The impact of PsA on finances may be through lost work productivity[155,156], direct medical costs, insurance and pension costs, and broader financial impact on the family. Up to 50% of people with PsA become unemployed and those able to attend work report reduced effectiveness (presenteeism).[157] A study of work disability observed treatment of active PsA was associated with a 40% improvement in work disability after six months treatment with biologic therapy.[158] In a Danish study of healthcare and public transfer (allowance) costs in patients with PsA reported the relative risk (RR) for being on disability pension five years prior to PsA diagnosis was 1.36 (95% CI 1.24 to 1.49) compared with the general population rising to 1.60 (95% CI 1.49 to 1.72) at the time of diagnosis and 2.69 (95% CI 2.40 to 3.02) 10 years after diagnosis, where 21.8% of the patients with PsA received disability pension.[159]

Psychological impact of PsA

People living with PsA suffer from a range of psychological impacts including disturbed sleep, fatigue, low-level stress, depression and mood/behavioural changes and poor body image/. Each individual respond to pain differently, depending on a variety of psychological factors including personality structure, cognition, and attention to pain.[155] Fatigue is now recognized as one of the core domains to be measured in RCTs for PsA, and have recognised to negatively impact to patients' QoL and work.[160–162] Anxiety and depression are known to be prevalent amongst people living with PsA. A recent systematic literature review of 24 studies and 31,227 people with PsA reported a pooled estimate of 33% (95%CI 17 to 53%) living with anxiety and up to 51% living with depression.[163]

Management of PsA beyond musculoskeletal domains.

The burden of PsA beyond musculoskeletal manifestation has been increasingly recognized. This highlighted the importance of a patient-centred holistic approach in the care of patients living with PsA. Different models of multi-disciplinary care lead by rheumatologist or dermatologist, together with specialized nurses, psychologists, and various therapists have been explored.[164] The evidence showing favourable outcomes are preliminary,[165] and further studies to better understand sustainable outcomes are required. Nonetheless, the awareness of the multi-dimensional needs of these patients remain the key to improving the care of these patients.

Box: patient experience

The advent of effective DMARDs has changed the perspective of people with PsA for the better. When I was diagnosed with PsA after a delay of 5 years suffering from severe psoriasis and unexplained joint pain, I was left with Indomethacin. It could not prevent serious damage of one knee, a radical synovectomy followed by a total knee replacement ten years later. I lost my job as a company trainer and became depressed, hardly able to take care of my family.
Starting anti-TNFα became a life-changing event. I joined a local patient hydrotherapy group and became a volunteer at an arthritis patient organization. I got to know other patients and their stories inspired me to read information about rheumatology research. It made me aware about my responsibility for my own health. Too long I had unconditionally followed my rheumatologist's ~~advices~~advice and still feeling isolated and loosing many friends. Receiving an effective treatment motivated me to give something back to society and changed my perspective on health care delivery and research. I learned the principles of self-management which enabled me to cope better with residual symptoms and limitations. For me remission is not the ultimate goal if that means to further increase the MTX dose. Communication with my rheumatologist is improved, I dare to ask more questions and we discuss existing guidelines. Sometimes a specialized arthritis nurse monitors my disease, and it is good to see that she not only asks how my joints are doing but also asks for skin symptoms.
Over the years the diagnosis and care of people with PsA has improved. I have developed a positive outlook on my future and, despite the fact that we haven't found the holy grail of curing the disease, I am optimistic about the perspective for newly diagnosed people that is promising.

Anon

Outlook

While the field of PsA has continued to evolve substantially over the last two decades, a number of outstanding gaps in basic, translational and clinical research remain unmet. There are several knowledge-based needs for further basic/translational advancement in the field. First, is the need for more detailed characterization of genetic and environmental factors that determine disease initiation.[42] Although several genome-wide association studies have contributed to the study of disease pathogenesis, multiple questions are yet to be answered, such as why the concordance rate for PsA is under 20% in monozygotic twins and what is the precise role of epigenetic modifications, environmental exposures, biomechanical stress and infections (including gut and skin dysbiosis) in the triggering of synovio-entheseal disease. Further, the cellular and molecular drivers of disease perpetuation remain to be fully elucidated. This is of high relevance because most of the latest advances in therapeutics derived from the discovery of a handful of unique, disease-specific targets, most notably IL-17 and IL-23 cytokines and/or their receptors. A more expansive and detailed characterization of T resident memory cells[52], innate cells (i.e., gamma delta, ILCs, NKs)[166] and newly discovered players should include not only their molecular and functional capacity, but also their spatial interactions, homing features and migratory patterns so that their presence in various compartments can be studied and therapeutically addressed.

Concomitantly, there are multiple challenges to be elucidated in the clinical realm. Those include the need for further characterization of factors associated with the development of PsA; the common definition of states that precede clinically overt synovio-enthesitis (i.e., what constitutes pre-clinical PsA); the meaning of imaging abnormalities present in patients with psoriasis without musculoskeletal symptoms[167,168]; the timing for potential immunomodulatory interventions and even preventive strategies[15]; and the distinction between various phenotypes of PsA from other forms of inflammatory arthritis (e.g., axial PsA from axial SpA).[169] Critically, and despite the achievement of remarkable outcomes in clearance of the skin with the newer generation of biologics (i.e., IL-23 and IL-17 blockers), the use of the same molecular strategies has not proven superior to TNF blockade when it comes to ameliorating peripheral arthritis or axial disease[170].

To overcome these challenges, multiple complementary and potentially synergistic priorities are envisioned. First, incorporating digital biomarkers into the clinical journey of patients with psoriatic disease should help address progression from psoriasis to PsA, flares and treatment response. Second, an in-depth study of cells and associated inflammatory mediators that modulate disease in the synovial, entheseal and axial tissues is gradually materializing. Several platforms promise to aid in this endeavour, including spatial transcriptomics[171], ECCITE-seq[172] and other variations of single cell resolution sequencing technologies. In turn, these can aid in precision medicine approaches and treatment strategies based on synovial biopsy and/or synovial fluid cellular/molecular pathways. Critically, big data analytics that incorporate clinical, genetics, environmental, and immunologic variables into predictive algorithms for diagnostics and therapeutics are emerging and should serve as examples for bringing precision medicine initiatives into PsA.

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As these tools become available, it will be of the essence to apply the knowledge generated into avenues for new therapeutic paradigms. As discussed, the current approach of monotherapy strategies to improve the outcomes of a multi-domain, multi-cytokine condition such as PsA may be inadequate. Altering the strategies to psoriatic therapeutics by implementing multi-target approaches may prove more efficacious.[173] This has been done with multiple neoplastic syndromes and is currently being tested in related conditions, such as IBD. A concrete example is the VEGA trial, which is testing the hypothesis that biologic combination of a TNF inhibitor and an IL-23 inhibitor will be superior to monotherapy.[174]

Ultimately, the success of these endeavours will be dependent on innovative work performed by clinical and translational researchers and industry partners most likely through team science approach. Multiple recent programs have been launched that incorporate private-public partnerships to advance the field through collaborative efforts, using novel multi-disciplinary strategies. These include the National Psoriasis Foundation's psoriasis preventive initiative (PPI); the European Union's Innovative Medicines Initiative (IMI)[175] [a partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA)]; and the Accelerating Medicines Partnership (AMP)[176], an NIH-led pre-competitive effort between government, industry, academia and non-profit organizations to harness collective capabilities, scale and resources toward the development of new therapies for

complex, heterogeneous diseases. All three programs have funded (or propose to fund) large consortia of investigators in the field which, combined with individual efforts, will be fundamental to enhance the understanding of PsA pathogenesis, diagnostics, and new targets for better treatments and even preventive strategies.

Tables

Table1:

Clinical, laboratory and radiographic features which help to distinguish early, active PsA from Rheumatoid Arthritis (RA), Osteoarthritis (OA) or Ankylosing Spondylitis (AS).

	PsA	**RA**	**OA**	**AS**
Polyarticular	Common	Very common	Common	Rare
Oligoarticular	Common	Occasional	Common	Occasional
DIP joint involvement	Common	Rare	Common	Rare
Axial Spondyloarthritis	Common	No	No	Nearly always
Dactylitis	Common	No	No	Rare
Enthesitis	Common	Rare	No	Common
Psoriasis	Very common	Rare	Rare	Occasional
Nail dystrophy	Very common	No	No	Occasional
RF ++	Occasional	Very common	Rare	Rare
aCCP +	~~Occasional~~Rare	Very Common	Rare	Rare
Elevated ESR/CRP	Common	Very common	Rare	Common
HLA-B27 positivity	Occasional	Rare	Rare	Very common
Joint erosion*	Common	Very common	Occasional	Occasional
Osteoproliferation*	Common	Rare	Common	Very common**
Sacroiliitis on radiographs*	Occasional	No	No	Nearly always

No = not found; Rare = <10%; Occasional = 10-30%; Common = 30-60%; Very common = 60-90%; Nearly always = >90%

*in disease >2 years duration

** very common in spine or sacroiliacs; occasional in peripheral skeleton

Table 2: Classification criteria for psoriatic arthritis and enthesitis-related arthritis: International Le of Associations for Rheumatology vs Vancouver criteria

ILAR Enthesitis-Related Arthritis	ILAR Psoriatic Arthritis	Vancouver Psoriatic Arthritis
Arthritis and Enthesitis OR Arthritis or Enthesitis plus at least 2 of the following: · Sacroiliac joint tenderness or inflammatory back pain · HLA-B27 positivity · Family history (first-degree relative) with HLA-B27 associated disease. · Acute and symptomatic anterior uveitis · Arthritis in a boy older than 6 y	Arthritis and Psoriasis OR Arthritis and at least 2 of the following: · Dactylitis · Nail pitting or onycholysis · Family history of psoriasis (first-degree relative)	Arthritis and Psoria OR Arthritis plus at least 2 of the following: dactylitis, nail pitting, family h of first-or-second d relative with psoria rash
Exclusions: psoriasis in self or first-degree relative, rheumatoid factor positivity, systemic JIA	Exclusions: Onset of arthritis in an HLA-B27 positive man after 6 y, family history (first-degree relative) with HLA-B27-associated disease, rheumatoid factor positivity, systemic JIA	Exclusions: None

~~**Table 2:**~~

Table 1
International League of Associations for Rheumatology classification criteria for enthesitis-related arthritis and psoriatic arthritis

Enthesitis-Related Arthritis	Psoriatic Arthritis
Arthritis and enthesitis OR Arthritis or enthesitis plus at least 2 of the following: ▪ Sacroiliac joint tenderness or inflammatory back pain ▪ HLA-B27 positivity ▪ Family history (first-degree relative) with HLA-B27–associated disease ▪ Acute and symptomatic anterior uveitis ▪ Arthritis in a boy older than 6 y	Arthritis and psoriasis OR Arthritis and at least 2 of the following: ▪ Dactylitis ▪ Nail pitting or onycholysis ▪ Family history of psoriasis (first-degree relative)
Exclusions: psoriasis in self or first-degree relative, rheumatoid factor positivity, systemic JIA	*Exclusions*: Onset of arthritis in an HLA-B27 positive man after age 6 y, family history (first-degree relative) with HLA-B27–associated disease, rheumatoid factor positivity, systemic JIA

Table 3:

Outcome Measures in PsA Clinical Trials[82-84]

Domains	Instruments
~~Joints~~Arthritis	68/66 T/S joint count, ACR20/50/70 response, DAS28, PsARC, PsAJAI, DAPSA, cDAPSA
Enthesitis	Leeds Enthesitis Index, SPARCC, MASES, 4-point*
Dactylitis	Leeds Dactylitis Index, Dactylitis Count, Dactylitis Severity Score
Axial Spondyloarthritis	BASDAI, BASFI, BASMI
Skin, nails	PASI, target lesion, physician global, PSI, PSD, NAPSI, mNAPSI, nail VAS
Composite – multi-domain	MDA, VLDA, PASDAS, CPDAI, GRACE
Pain	VAS, NRS
Patient global	VAS (joint global, skin + joints global), NRS
Physician global	VAS (joint global, skin + joints global), NRS
Physical Function	HAQ, HAQ-S, ~~PSAID,~~ SF-36 PF, PROMIS-PF
HRQoL	SF-36, PSAID, PsAQoL, DLQI, EQ-5D, PROMIS-Profiles
Fatigue	FACIT-Fatigue, VAS, PROMIS-Fatigue
Participation	PROMIS-Social Roles and participation
~~Enthesitis~~	~~Leeds, SPARCC, MASES, 4-point~~
~~Dactylitis~~	~~Leeds Dactylitis Index, Dactylitis Count, Dactylitis Severity Score~~
Acute phase reactant	ESR, CRP
~~Imaging~~Structural damage	X-ray (modified Sharp or van der Heijde–Sharp), MRI, US
Work/home productivity	WPAI, WPS

HRQoL, Health-Related Quality of Life; ACR, American College of Rheumatology; DAS, Disease Activity Score; PsARC, Psoriatic Arthritis Response Criteria; PsAJAI, Psoriatic Arthritis Joint Activity Index; DAPSA, Disease Activity in Psoriatic Arthritis; cDAPSA, clinical Disease Activity in Psoriatic Arthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; PSD, Psoriasis Symptom Diary; NAPSI, Nail Psoriasis Severity Index; mNAPSI, Modified Nail Psoriasis Severity Index; VAS, visual analogue scale; MDA, Minimal Disease Activity; VLDA, very low disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; CPDAI, Composite Psoriatic Disease Activity Index; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; GRACE, GRAPPA Composite Exercise; NRS, numeric rating scale; HAQ, Health Assessment Questionnaire; HAQ-S, Health Assessment Questionnaire-

Spondyloarthritis; PSAID, Psoriatic Arthritis Impact of Disease; SF-36, Short Form 36; PsAQoL, Psoriatic Arthritis Quality of Life Index; DLQI, Dermatology Life Quality Index; FACIT, Functional Assessment of Chronic Illness Therapy; SPARCC, Spondyloarthritis Research Consortium of Canada; MASES, Maastricht Ankylosing Spondylitis Enthesis Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; MRI, Magnetic resonance imaging; US, Ultrasound; WPAI, Work Productivity and Activity Index; WPS, Work Productivity Survey.

* Used in the impact study

Table 4:

PsA Therapeutic Groups[5]

- Adjunctive therapies
  - NSAIDs, glucocorticosteroids [po, ia, topical]
- Conventional synthetic DMARDs (cs-DMARDs)
  - Methotrexate, sulfasalazine, leflunomide, Cyclosporine
- bDMARDS
  - TNF inhibitors (TNFi)
    - Etanercept*, infliximab*, adalimumab*, golimumab, certolizumab
  - IL12/23i
    - Ustekinumab
  - IL17i
    - Secukinumab, ixekizumab, brodalumab ^, bimekizumab#
  - IL23i
    - Guselkumab, risankizumab^, tildrakizumab^
  - T cell modulator
    - Abatacept
- Targeted synthetic DMARDs (ts-DMARDs)
  - PDE4i (apremilast)
  - JAKi (tofactinib, upadacitinib; baricitinib#, , filgotinib#)

(*biosimilars available in 2021; ^approved for psoriasis, not PsA, in 2021; #in development)

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Figure 1: Stages in the evolution of Pso to PsA. These stages include: ① patients with skin and/or nail psoriasis only but with risk factors, at present indeterminate, for subsequent development of PsA; ② MSK immune activation phase when there is evidence of cytokine (e.g. IL-23/IL-17 and/or TNF) over-production at a cellular or tissue level; ③ a stage where there is asymptomatic evidence of synovio-entheseal inflammation on imaging: MRI or ultrasound; ④ a "prodromal stage" where psoriasis patients may have MSK symptoms such as arthralgia and/or stiffness but without sufficient signs to make a diagnosis of PsA; and ⑤ PsA meeting CASPAR criteria. The bidirectional arrows in Figure 1 reflect the important possibility that some of these stages may be reversible. At present, treatment is focused on those patients who receive a PsA diagnosis (stage ⑤ in Figure 1) and have ongoing inflammatory disease and evidence of radiographic damage. Future treatment intervention strategies may target patients at an earlier disease stage (1-4).

Figure 2.
Distinct clinical phenotypes of psoriatic disease (PsD) occur as a consequence of genetic predisposition, environmental triggers (such as biomechanical or metabolic stress, infections and obesity) and local factors according to disease site (joints, skin, spine or entheses). Amplification of the IL-23–IL-17 axis is initiated via activation of innate cells in the skin, entheses and gastrointestinal tract, ultimately resulting in the expansion of CD4+ and CD8+ T helper 1 (TH1) and TH17 cells, which are expanded by IL-23 and IL-12 and produce TNF and IL-17. Different HLA alleles and/or haplotypes, T cell subsets and treatment response profiles are associated with different PsD phenotypes. Synovial-predominant PsD is associated with HLA-B*08:01:01, HLA-C*07:01:01 and haplotype HLA-B*08:01:01–HLA-C*07:01:01, CD8+ engagement with TH1 cells and responsiveness to TNF inhibition. Cutaneous-predominant PsD is associated with HLA-B*57:01 and HLA-C*06:02, TH1 cell-driven and responsive to IL-17 and IL-23 inhibition. Entheseal-predominant with or without axial disease, which is associated with the HLA-B*27:05:02 allele, involves engagement of both TH1 and TH17 cells that produce both TNF and IL-17, and is responsive to TNF and IL-17 inhibition. Psoriatic arthritis mutilans (PAM) likely represents a combination of these host genetic factors and T cell interactions. CXCR3, CXC-chemokine receptor 3; CCR, CC-chemokine receptor; IL-12R, IL-12 receptor; IL-23R, IL-23 receptor. (From ref 42, with permission)

Figure 3. The complex model of quality of life for patients with PSA.

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